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Urinary Cotinine and Parent History (Questionnaire) as Indicators of Passive Smoking and Predictors of Lower Respiratory Illness in Infants

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Summary. Studies of the effects of passive smoking on lower respiratory illness (LRI) have relied on questionnaires to measure exposure. We studied the association between two measures of passive smoking and the incidence of acute LRI in infants. We analyzed data from a community-based cohort study of respiratory illness during the first year of life in North Carolina. The incidence of LRI was determined by telephone calls at 2-week intervals. Environmental, demographic, and psychosocial risk factors for LRI were measured during home interviews. Tobacco smoke exposure was measured as the mean number of cigarettes smoked per day in the infant's presence. Smoke absorption by the infants was measured by the urinary cotinine/creatinine ratio.

Of the 485 infants in the study, 325 (67%) had telephone follow-up and at least two home interviews. In bivariate analyses, reported tobacco smoke exposure and urinary cotinine were associated with LRI. Only the association between reported exposure and LRI remained significant after adjusting for confounders. [adjusted incidence of LRI (episodes/child-year) nonexposed: 0.6; ≤10 cigarettes/day: 0.9 (RR 1.5, 95% CI: 1.1, 2.0); >10 cigarettes/day: 1.3 (RR 2.2, 95% CI: 1.3, 3.8)]. We conclude that infants reportedly exposed to tobacco smoke have an increased incidence of LRI. There are differences between questionnaire and biochemical measures of passive smoking. Urinary cotinine will not necessarily improve the validity of studies of the relationship of passive smoking to LRI in infants. **Pediatr. Pulmonol. 1997; 23:417–423.**

Key words: lower respiratory illness; environmental tobacco smoke; cotinine.

INTRODUCTION

Numerous studies have suggested that passive smoking is associated with an increased occurrence of LRI. To measure passive smoking, most studies have relied on questioning caretakers about the amount of smoke produced in the child's environment.[1,2] The use of cotinine, a major metabolite of nicotine, as a biologic marker of smoke-absorption has been suggested as an approach to strengthen the evidence of a relationship between passive smoking and respiratory illness. However, the relationship of cotinine to LRI in infants is unknown, and the types of studies in which cotinine will be most useful remain unclear.

Urinary cotinine is a potentially attractive addition to epidemiologic studies because it may more accurately account for environmental characteristics that determine how much tobacco smoke is absorbed (e.g., the proximity of the smoker to the child, the concentration of smoke in the room) and because it might avoid potential bias

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when parents deny smoke exposure that actually took place. However, there are a number of potential problems with its use. Urinary cotinine excretion varies considerably among persons exposed to similar amounts of nicotine.[3] Cotinine has a half-life of about 20 hours and therefore reflects absorption of smoke resulting from exposure to tobacco smoke only within the previous few days.[4] If the effects of tobacco smoke are related to chronic smoke exposure, urinary cotinine may be less strongly associated with LRI. Little is known about the pathogenesis of the impact of tobacco smoke on the lung. Nicotine is only one of thousands of compounds in tobacco smoke and may not be responsible for the health effects of passive smoking. Finally, cotinine is expensive to measure, and it may be difficult to obtain samples from infants in large-scale epidemiologic studies.

The objective of this study was to examine the association between two measures of passive smoking (maternal reports of tobacco smoke exposure and urinary cotinine) and the incidence of acute LRI in infants. Because investigators are now expected to consider the use of biomarkers as measures of passive smoking, our results could be helpful to those studying the consequences of passive smoke exposure on infants.

MATERIALS AND METHODS

Study Sample

We analyzed data from the control group of a community-based randomized trial designed to study the effects of an intervention to reduce infants' exposure to tobacco smoke and, thereby, their rate of lower respiratory illness in the first year of life.[5] The design of the primary study, and the findings about program impact have been described elsewhere.[6] The study involved infants born in Alamance and Chatham counties, North Carolina, between 1986 and 1988. To be eligible for enrollment, an infant had to have no significant postnatal problems and a birth weight of at least 2,000 g. At the time of recruitment, families were told only that the study was intended to investigate infant health during the first year of life.

Measurement of Potential Risk Factors for LRI

Data about potential risk factors for LRI were collected during home interviews. Information was elicited by questionnaires administered to the infants' mothers and included demographic characteristics as well as detailed environmental and psychosocial characteristics. This information included socioeconomic status, enrollment in day care, household crowding, exposure to a woodstove, type of feeding, mothers' psychological stress, a family history of allergy, and the season of infant's birth. All variables were measured at the 3 week home interview except day care attendance, which was measured at the 12 month home interview.

Abbreviations

CI	Confidence interval
GEE	Generalized estimating equation
LRI	Lower respiratory illness
RR	Relative risk
SES	Socioeconomic status

Measurements of Passive Smoking

Two measures of passive smoking were obtained in this study. *Smoke exposure* was measured as the average number of cigarettes smoked per day in the infant's presence during the week before each home interview. This was calculated by multiplying the number of cigarettes per day smoked in the infant's presence during a "typical" day of the previous week by 5 and adding the number of cigarettes smoked in the infant's presence during the previous weekend. The total was then divided by 7. A cigar or a pipeful was considered equivalent to one cigarette. This measure is described in detail elsewhere.[7]

Smoke absorption takes place when an infant has sufficient contact with tobacco smoke to result in the absorption of nicotine. It was measured as the urinary concentration of cotinine expressed as the cotinine/creatinine ratio (ng cotinine/mg creatinine). Urine for measurement of continine was collected at the 3 week, 6 month, and 12 month home visits. Our laboratory procedures for the radioimmunoassay of cotinine and dry chemistry methods for creatinine have been reported.[5] Parents were told that the urine specimens were being collected to measure tobacco smoke exposure. Questions about tobacco smoke exposure were asked after the urine bag was placed on the infant. In previous studies, we had found that the correlation between reported exposure to tobacco smoke and urinary cotinine was not improved by adjusting for characteristics of the home environment such as size of the room or its ventilation.[8]

Information on mothers' smoking during pregnancy was obtained as supplemental information after the study began. This information was missing for 24% of mothers. Although maternal smoking during pregnancy was highly correlated with maternal smoking during the first year of the infants' life (phi coefficient = 0.78), it was not highly correlated with the measure of smoke exposure (exposure to tobacco smoke from all sources) (phi coefficient = 0.28). Maternal smoking during pregnancy was also not correlated with urinary cotinine (phi coefficient = 0.25). We decided not to include information about prenatal smoke exposure in analyses because the information was not collected on all mothers in the

sample and because the correlation of prenatal smoking with the measures of smoke exposure and smoke absorption (urinary cotinine) was weak.

Measurement of LRI

Symptoms of acute LRI were measured by telephone calls to the families every 2 weeks. An acute LRI was defined as the parents' report of the presence of cough, wheezing, and rattling in the chest. This definition was found to have a sensitivity of 88% and a specificity of 68% when compared with a physician's diagnosis.[9] These test characteristics are similar to those reported by others.[10] The incidence of acute LRI was expressed as the number of episodes of LRI per child-year at risk.

The study was approved by the Committee on Research Involving Human Subjects of The University of North Carolina School of Medicine.

Statistical Analyses

To examine the relationship between LRI and passive smoking, we considered the time-dependent nature of the two passive smoking measures (exposure to environmental tobacco smoke and urinary cotinine) and two of the covariates (age and season) of both, as well as the effects of the following additional risk factors for LRI: education of the head of the household, the infant's birth weight, maternal age, household crowding, type of feeding (breast or bottle), gender, race, family history of allergy or respiratory illness, and day care attendance. The categorization of confounding factors in the models was based on previous examination of these variables and is reported elsewhere.[9]

We defined broad categories for reported exposure to environmental tobacco smoke (0, 1–9 cigarettes/day, >10 cigarettes/day) and urine cotinine (0, ≤120 ng/mg creatinine, >120 ng/mg creatinine) because for both variables, the relationships with LRI depended on the number or position of cut-off points. The cut-off point for the number of cigarettes smoked per day was based on its clinical sensibility (≤1/2 pack, >1/2 pack). Among infants with cotinine in their urine, the median was selected as the cut-off point. We used measurements of passive smoking at the 3 week home interview to estimate the incidence of LRI during the *first* 6 months of life and measurements at the 6 month home interview for estimates in the *second* 6 months. Passive smoking measurements were missing at the 6 month home interview in 58 cases (18%); we substituted values from the 12 month visit for these subjects. Our previous studies of infants in this cohort indicated that reported exposure to tobacco smoke increases from birth to 6 months of age and remains relatively stable during the second 6 months of life.[9]

The time-varying covariates, age and season, were recorded at the biweekly telephone interviews. A child's age was categorized into three groups (<4 months, 4–8 months, and >8 months) to reflect changes in the risk of LRI during the first year of life. Seasons were defined as respiratory (October–April) or non-respiratory (May–September). It was not possible to treat day care as a time-varying covariate because we did not have information about when children started in day care and because almost all children in day care at 6 months were also in day care at 12 months.

We developed separate Poisson regression models to examine the relationship between LRI and the two passive smoking measures. For each child, we counted the episodes of LRI and days at risk within each age, season, and passive smoking cell. The log of the LRI counts was modeled using days-at-risk as a fixed covariate. Because each child contributed to multiple observations, we fit the models using GEE methods, assuming equal correlations among repeated measures.[11–13]

In developing the final models, we considered the potential for effect modification and confounding. All two-way interactions between the risk factors and tobacco smoke exposure variables, as well as one three-way interaction among tobacco smoke exposure, SES, and day care, were insignificant at the 0.10 level (Wald chi-square).[9] Main effects for risk factors were retained in the model if they were significant at the 0.10 level, or if they appeared to be confounders. Variables that were associated with a meaningful change in the odds of LRI were included in the final model. The final models were used to estimate the incidence of LRI per child year.

RESULTS

Study Sample

There were 2,332 births in which the infant was eligible to participate in the intervention trial. Of the eligible families, 1,217 (52%) agreed to enroll. Study infants were more likely to be of high socioeconomic status and less likely to have mothers who smoked than infants not enrolled.[9] Of the 485 infants who were randomized to the control group, 325 (67%) had a 3 week home visit, telephone follow-up, and at least one other home interview. These infants comprised the study sample for the analyses in this paper. Differences between the study sample and infants who failed to complete the study and families without telephones have been reported previously.[9]

Passive Smoking

In the study sample, 182 (56%) infants were exposed to tobacco smoke according to maternal reports. Infants exposed to tobacco smoke were more likely to be bottle-

TABLE 1—Prevalence of Risk Factors for Lower Respiratory Illness in Infants Exposed and Not Exposed to Tobacco Smoke

	% Exposed (n = 182)	% Not exposed (n = 143)
Demographics		
Male	54.4	47.6
White	63.7	82.5
Born in non-respiratory season	45.1	43.4
Education (head of household)		
High school	41.8	19.6
>High school	35.2	69.9
Environmental data		
Bottle fed	67.6	36.6
Household crowding	–	
(>0.5 person/room)	58.9	41.3
Gas cooking	9.9	7.7
Woodstove	5.7	13.6
Day care	40.1	37.8
Familial data		
History of allergy	27.8	30.7
History of respiratory disease	19.7	12.7
Stress	11.5	3.5

fed, had less educated heads of the household, and lived in crowded households (Table 1). Median urinary cotinine levels were highest among infants when both the mother and other household members ("others") smoked, lower in infants reportedly exposed to either smoking mothers or to other household members who smoked, and lowest in those who had no household smokers (Fig. 1). Urinary cotinine excretion varied over the three measurement periods. Reported exposure was also highest among infants when both mothers and other household members smoked and lower among infants exposed to either smoking mothers or other household members (Fig. 2). Unlike the pattern observed for the measure of smoke absorption, reported exposure to tobacco smoke remained relatively constant over the three measurement periods.

We found little relationship between urinary cotinine excretion and the amount of environmental tobacco smoke to which an infant was reportedly exposed (Fig. 3). The correlation coefficient between reported tobacco smoke exposure and infants' urinary cotinine measurements was 0.47 at the first measurement and 0.33 at the second measurement.

Relationship of Passive Smoking to LRI

We used GEE Poisson regression models to estimate the incidence of LRI using both questionnaire and cotinine measures of passive smoking. In bivariate analyses, both measures of passive smoking had a dose-response relationship with the incidence of LRI (Table 2, unadjusted models). The final models were then adjusted for season of birth, the infant's age, socioeconomic status,

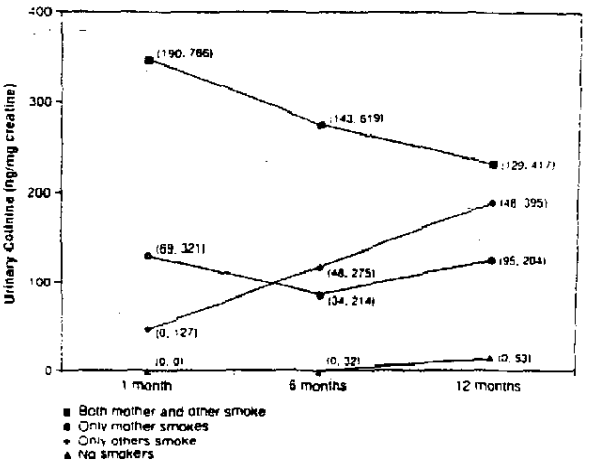

Fig. 1. Median urinary cotinine levels in infants.

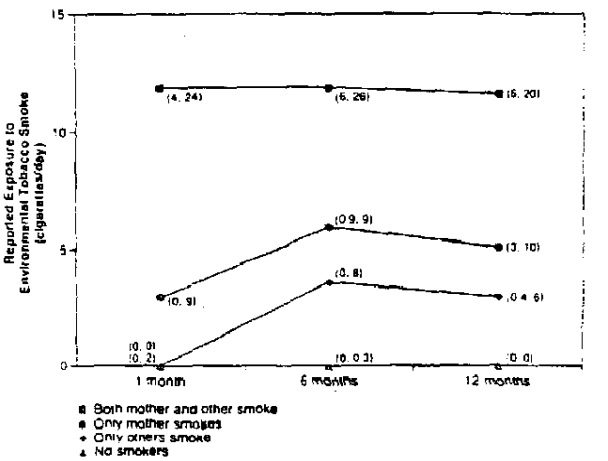

Fig. 2. Exposure of infants to tobacco smoke.

household crowding, and day care. In the model using maternal reports of tobacco smoke exposure, the incidence of LRI was: 0.60 episodes/child year among infants not reportedly exposed to tobacco smoke, 0.89 episodes/child-year among those reported to be exposed to ≤10 cigarettes/day (RR 1.5, 95% CI: 1.1, 2.0), and 1.3 episodes/child-year among those exposed to >10 cigarettes/day (RR 2.2, 95% CI: 1.3, 3.8). In contrast, the association between urinary cotinine and LRI was no longer significant after adjustment for other LRI risk factors (Table 2).

We also assessed whether the use of both measures of passive smoking together would be more closely associated with rates of LRI than either measure alone. The incidence densities computed from the model with both variables and their interaction were similar to those from the model with reported tobacco smoke exposure alone.

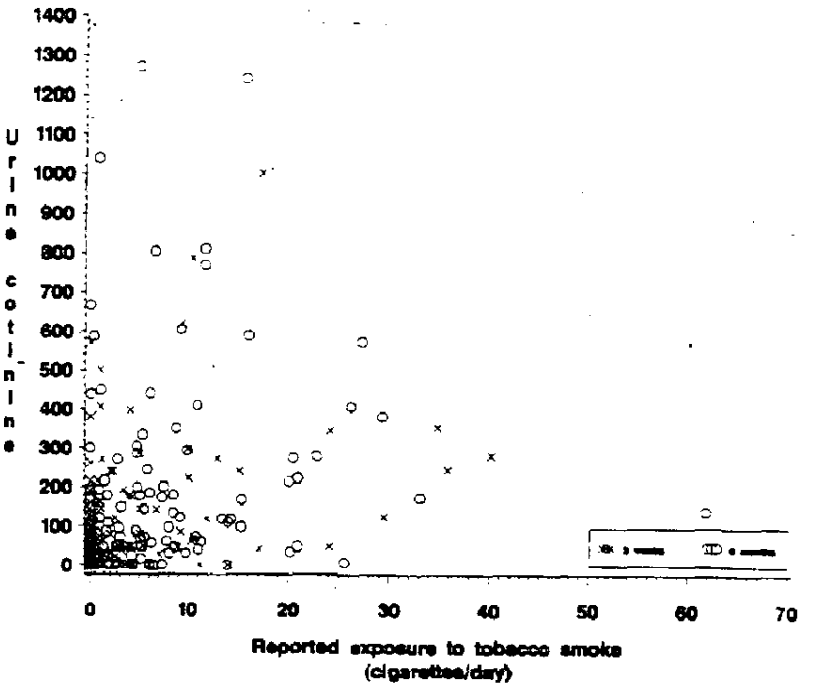

Fig. 3. Relationship of urinary cotinine excretion and the amount of environmental exposure in infants.

TABLE 2—Effect of Passive Smoking on Lower Respiratory Illness Incidence (Episodes LRI/child-year)

	Unadjusted model		Adjusted model[1]			
	Incidence	(95% CI)	Incidence	(95% CI)	RR	(95% CI)
Reported exposure						
Not exposed	0.68	(0.53, 0.88)	0.6	(0.30, 1.2)	—	
≤10 cigarettes/day	1.1	(0.85, 1.3)	0.89	(0.42, 1.9)	1.5	(1.1, 2.0)
>10 cigarettes/day	1.6	(1.1, 2.4)	1.3	(0.54, 3.2)	2.2	(1.3, 3.8)
Overall *P* value (χ^2)	0.001		0.006			
Urine cotinine (ng/mg creatinine)						
0	0.67	(0.50, 0.89)	0.64	(0.37, 1.1)	—	
≤120	0.99	(0.56, 1.7)	0.82	(0.41, 1.6)	1.3	(0.8, 2.1)
>120	1.1	(0.63, 1.9)	0.88	(0.46, 1.7)	1.4	(0.9, 2.1)
Overall *P* value (χ^2)	0.02		0.2			

[1]Model adjusted for season, age, SES, household crowding, family history of respiratory disease, day care.

However, the precision of the estimates was lower in the model with both exposure variables.

DISCUSSION

Our results confirm the association of passive smoking with an increased incidence of lower respiratory illness in infants in the first year of life. In addition, we found a dose-response relationship with LRI when passive smoking is measured by parental report of exposure to tobacco smoke or by urinary cotinine. However, only the relationship between reported exposure and LRI remained statistically significant after adjustment for confounding factors. In infants, urinary cotinine does not appear to add to the assessment of the relationship between passive smoking and LRI.

Over the past 20 years, numerous studies have documented the effect of exposure to tobacco smoke on the risk of lower respiratory illness in infants [1–6]. Most studies have measured the occurrence of LRI by asking parents about the presence of chronic respiratory symptoms or asking about episodes of LRI symptoms that took place over extended time periods (e.g., during the past year). Such results may be influenced by a tendency to remember only particularly severe or persistent episodes of illness. Our study extends the results of previous

work because it is based on *prospective* assessment of exposure and outcome. It provides an estimate of the relationship of passive smoking to the incidence of LRI that takes into account the influence of multiple episodes of illness in individual infants.

There are limitations in using parent reports to measure passive smoking. If smokers underestimate their children's exposure to tobacco smoke, less of a dose-response gradient might be observed; children exposed to heavy smokers would have been included in a category of moderate smoke exposure. Alternatively, smoking parents might be more likely to report lower respiratory symptoms in their children if they were familiar with the negative health effects of passive smoking. This would have spuriously increased the association between passive smoking and LRI as measured by parents' reports. The consistency of our findings with studies conducted before the health effects of passive smoking were widely publicized makes this last explanation less likely.

We did not find a statistically significant relationship between urinary cotinine and LRI after adjusting for confounders. However, the direction of the relationship was consistent with other studies in which elevated cotinine levels were associated with bronchiolitis in hospitalized infants,[17] otitis media in toddlers,[18] asthma in children,[19] and lung function in school-age children.[20] Like most other studies of LRI in infants, ours was limited by using reports of symptoms to diagnose LRI. The use of symptoms as a marker of LRI presumably results in some random misclassification or "*noise*" in the measurement of LRI and most likely produces an underestimate of the effects of passive smoking. It is possible that previous investigations have observed a stronger relationship between urinary cotinine and respiratory illness because they studied more serious illness, or diseases that can be measured more specifically than LRI. However, data from these studies have not indicated that cotinine is more strongly associated with respiratory illnesses than reported exposure.

Another explanation for the weaker association between urinary cotinine and LRI may be that the measurement of cotinine is not reliable. Characteristics of the home environment, such as ventilation and proximity to the smoker, have been shown to be related to variability of urinary cotinine.[4,21] These studies have also demonstrated marked intra-individual variation in cotinine.[21] Variability may also result from physiologic and developmental changes that take place during the first year of life, such as increases in infants' ability to metabolize and excrete cotinine, and increased motor skills that may allow infants to come into less contact with tobacco smoke. Such increased mobility may explain the changes in urinary cotinine we observed among infants exposed to different sources of environmental tobacco smoke. It may be necessary to obtain multiple measures of urinary cotinine to reduce this variability. Such repeat measurements may not be feasible in large community-based studies like ours.

Hulka and Margolin[22] have suggested that biomarker and questionnaire measures of exposure can be expected to have different relationships with health outcomes in epidemiologic studies because they may be measuring different biologic relationships. Studies of the impact of passive smoking on respiratory disease are limited by a lack of knowledge about the pathologic relationship between tobacco smoke and respiratory disease. The health effects of tobacco smoke are probably produced by the direct local effect of smoke on the lung rather than through the absorption of nicotine. Thus, it is not surprising that we found the relationship between smoke exposure and LRI to differ from the relationship of smoke absorption and LRI. Our results indicate that the use of urinary cotinine will not necessarily improve the validity of epidemiologic studies of the relationship of passive smoking to lower respiratory illness in infants. In selecting a measure of passive smoking, it is necessary to consider the potential costs of measuring nicotine absorption (i.e., the logistical challenges of repeated cotinine determinations in infants and the expense of analysis), as well as the potential contribution cotinine measurements would have on the validity of the study's results. The utility of measuring this biomarker will depend on the study's overall goals.

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